REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

The March 15, 2005, personal interview between Examiner Hutson and applicants' undersigned attorney is gratefully acknowledged. The substance of that interview is summarized below.

The objection to the specification for entry of new matter is respectfully traversed in view of the above amendments.

The rejection of claims 25, 26, and 29 under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) for obviousness over U.S. Patent No. 6,361,996 to Rao et. al. ("'996 Patent") is respectfully traversed.

The '996 Patent has been fully discussed in previous responses to office actions. Accompanying this amendment is the Second Declaration of Mahendra S. Rao, M.D., Ph.D. Under 37 C.F.R. § 1.132 ("Second Rao Declaration"). The declarant is the same Dr. Rao who is the co-inventor of the '996 Patent. His declaration is presented to demonstrate why the subject matter of the '996 Patent is very different from that of the present patent application (Second Rao Declaration ¶ 5).

It is the position of the U.S. Patent and Trademark Office ("PTO") that the '996 Patent inherently discloses the claimed oligodendrocyte-specified progenitor cells of the present application. In particular, the PTO asserts that the '996 Patent's multipotential oligodendrocyte-astrocyte precursor cells must inherently differentiate to the claimed oligodendrocyte-specified progenitor cells before further differentiating to mature oligodendrocytes. Applicants respectfully disagree.

As shown in Figures 1-2 of the '996 Patent, the astrocyte/oligodendrocyte precursor cells 14 and 54, respectively, differentiate directly into two cell types—i.e., astrocytes and oligodendrocytes (Second Rao Declaration ¶ 7). It is also known from clonal analysis that there is a homogenous population of astrocyte/oligodendrocyte precursor cells in which individual cells generate oligodendrocytes and two kinds of astrocytes by the process described in the '996 Patent (Id.). It is important to note that multiple pathways to generate post-mitotic, mature oligodendrocytes, have been described (Id.). Anderson and colleagues have shown that an oligodendrocyte/motorneuron precursor exists that does not make astrocytes (Zhou et al., "The bHLH Transcription Factors OLIG2 and OLIG1 Couple Neuronal and Glial Subtype Specification," *Cell* 109:61-73 (2002)) (Id.). Other investigators

have shown distinct sites of origin of oligodendrocytes and astrocytes presumably from separate precursors (Vallstedt et al., "Multiple Dorsoventral Origins of Oligodendrocyte Generation in the Spinal Cord and Hindbrain," *Neuron* 45:55-67 (2005) and Cai et al., "Generation of Oligodendrocyte Precursor Cells from Mouse Dorsal Spinal Cord Independent of *Nkx6* Regulation and *Shh* Signaling," *Neuron* 45:41-53 (2005)) (Id.). Yet other investigators have shown that different kinds of oligodendrocyte progenitors exist (Pringle et al., "*Fgfr3* Expression by Astrocytes and Their Precursors: Evidence that Astrocytes and Oligodendrocytes Originate in Distinct Neuroepithelial Domains," *Development* 130:93-102 (2003)) (Id.). Dr. Rao is not aware of any evidence that the astrocyte/oligodendrocyte precursor cells of the '996 Patent generated mature oligodendrocytes by way of an intermediate oligodendrocyte-specific precursor (Id.). Indeed, Gregori et al., "The Tripotential Glial-Restricted Precursor (GRP) Cell and Glial Development in the Spinal Cord: Generation of Bipotential Oligodendrocyte-Type-2 Astrocyte Progenitor Cells and Dorsal-Ventral Differences in GRP Cell Function," *J. Neurosci.* 22(1):248-256 (2002) have suggested that the '996 patent describes a glial progenitor that gives rise to a more restricted astrocyte/oligodendrocyte precursor that still directly makes predominantly astrocytes and a small minority of oligodendrocytes (Id.). Thus, cells in the '996 Patent's pathway to oligodendrocyte production are bi-potential astrocyte/oligodendrocyte progenitor cells that have strong astrocytic bias (Id.). These cell types are very different from the oligodendrocyte-specified progenitor cells of the present application.

During the March 15, 2005, personal interview, Examiner Hutson characterized the pending claims as being akin to product-by-process claims where patentability must be established, in accordance with the Manual of Patent Examining Procedure ("MPEP") § 2113, by the structure of the claimed product and not by the steps of making it except if those steps imply structure. Pursuant to MPEP § 2113, the PTO "bears a lesser burden of proof in making out a case of *prima facie* obviousness for product-by-process claims . . . than when a product is claimed in the conventional fashion." "Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product." MPEP § 2113.

Whether the analogy of the claimed invention to product-by-process claims is apt is questionable. In any event, assuming that the present claims can be regarded as product-by-process claims, applicants have clearly met their responsibility to establish patentability over the '996 Patent. In particular, to the extent the PTO has made a *prima facie* case of unpatentability, applicants have clearly presented evidence (i.e. the Second Rao Declaration) demonstrating otherwise. As the PTO is fully aware, Dr. Rao is the first-named inventor of the '996 Patent and would know far better than the PTO what the character of the cells disclosed in that reference are. Simply put, the Second Rao Declaration clearly demonstrates that the PTO's position that the claimed oligodendrocyte-specified progenitor cell is inherently present in the '996 Patent is wrong. Having demonstrated this, the PTO must provide countervailing evidence (rather than mere argument or speculation) and, in the absence of such evidence, must allow pending claims 25, 26, and 29.

Even if, assuming *arguendo*, the PTO can properly maintain its inherency position, which it cannot, claim 26 is nevertheless still patentable over the '996 Patent. In particular, as set forth in the October 14, 2004, Declaration of Mahendra S. Rao, M.D., Ph.D. Under 37 C.F.R. § 1.132 ("First Rao Declaration"), the adult progenitor cells of claim 26 possess an unobvious difference from the fetal-derived cells of the '996 Patent. This has been completely overlooked in the outstanding office action.

The '996 Patent is directed to the enrichment of glial progenitor cells from newborn rat brain (First Rao Declaration ¶ 8). Newborns have an abundant population of still-developing oligodendrocyte progenitor cells that may constitute a significant fraction of all of the cells in neonatal brain tissue (Id.). Yakovlev, et. al., "A Stochastic Model of Brain Cell Differentiation in Tissue Culture," *J Math Biol.*, 37(1):49-60 (1998); Bogler et. al., "Measurement of Time in Oligodendrocyte-type-2 Astrocyte (O-2A) Progenitors is a Cellular Process Distinct from Differentiation or Division," *Dev Biol.*, 162(2):525-38 (1994); and Raff et. al., "Platelet-derived Growth Factor From Astrocytes Drives the Clock That Times Oligodendrocyte Development in Culture." *Nature* 333(6173):562-65 (1988) describe cell cycle changes as glial progenitor cells mature (Id.). They showed that adult cells differ in their cell cycle time and the number of divisions before they will become postmitotic (Id.). The present patent application discloses this for adult human-derived cells (Id.). In addition, adult-derived human oligodendrocyte progenitor cells differentiate as oligodendrocytes and produce myelin much more quickly than do fetal or neonatal oligodendrocyte progenitor cells (Id.). As recently reported in Nunes et al., "Identification and Isolation of Multipotent Neural

Progenitor Cells from the Subcortical White Matter of the Adult Human Brain," *Nature Medicine* 9:239-247 (2003) and Windrem et al., "Fetal and Adult Human Oligodendrocyte Progenitor Cell Isolates Myelinate the Congenitally Dysmyelinated Brain," *Nature Medicine* 10:93-97 (2004), adult-derived oligodendrocyte progenitor cells not only myelinate much more rapidly than do fetal oligodendrocyte progenitors, but they do so more efficiently, with a higher proportion exhibiting effective myelin production, and myelinating a greater number of neuronal axons per donor cell than their fetal-derived counterparts (Id.). Adult cells are thus fundamentally more biased towards generating oligodendrocytes, towards maturing to express myelin proteins, and towards myelinating host axons (Id.). Moreover, adult cells execute all of these functions, and achieve each of these cellular milestones, much more quickly than fetal cells (Id.). As a result, they lend themselves to a very different set of potential clinical targets than fetal or neonatal-derived progenitors, as reported in Roy et al., "Progenitor Cells of the Adult Human Subcortical White Matter In: *Myelin Biology and Disorders*, vol. 1. R. Lazzarini, ed. Elsevier:Amsterdam, pp. 259-287 (2004) (Id.). Adult oligodendrocyte progenitor cells are thus fundamentally different from fetal or neonatal-derived progenitors (Id.). Thus, the '996 Patent's rat fetal astrocyte/oligodendrocyte precursor cells are very different from the adult oligodendrocyte progenitor cells in claim 26 of the present application (Id.). Accordingly, claim 26 should be allowed even if for some reason claims 25 and 29 cannot be allowed.

For all of these reasons, the rejection of claims 25, 26, and 29, based on the '996 Patent, should be withdrawn.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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